SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug Eluting Coronary Stent System (NIQ)
Device Trade Name:	XIENCE nano™ Everolimus Eluting Coronary Stent System (2.25 mm)
Device also distributed as:	PROMUS Everolimus Eluting Coronary Stent System
Applicant's Name and Address:	Abbott Vascular 3200 Lakeside Drive Santa Clara, CA 95054
Date of Panel Recommendation:	none
Premarket Approval Application (PMA) Number:	P070015/S054
Date of FDA Notice of Approval:	May 24, 2011
Expedited:	Not Applicable

The original PMA for the XIENCE V® Everolimus Eluting Coronary Stent System (XIENCE V Stent System) was approved on July 2, 2008 (P070015). The XIENCE V Stent System is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm. The SSED to support the initial approval is available on the CDRH website and is incorporated by reference here: http://www.accessdata.fda.gov/cdrh_docs/pdf7/P070015b.pdf.

This PMA supplement, P070015/S054, was submitted to support approval of the 2.25 mm diameter XIENCE V stent and expansion of the indications of the product, specifically, for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of ≥ 2.25 mm to <2.50 mm. The 2.25 mm diameter XIENCE V Stent System will be referred to as the XIENCE nano™ Everolimus Eluting Coronary Stent System (XIENCE nano Stent System).

II. INDICATIONS FOR USE

The XIENCE V Everolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.25 mm to 4.25 mm.

III. CONTRAINDICATIONS

The XIENCE V stent is contraindicated for use in patients:

- Who cannot receive anti-platelet and/or anti-coagulant therapy
- With lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system
- With known hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the XIENCE V Stent System labeling.

V. DEVICE DESCRIPTION

The components and characteristics of the XIENCE nano Stent System are identical to the XIENCE V Stent System approved in P070015. Please refer to the description provided in the original SSED for additional details. The characteristics of the XIENCE V Stent System are described in Table 1 below.

The XIENCE V Stent System (2.5mm – 4.0 mm) and XIENCE nano (2.25mm) (hereinafter referred to as XIENCE V stent or XIENCE V Stent System) is a device/drug combination product comprised of two regulated components:

- A device (MULTI-LINK VISION® Coronary Stent System or MULTI-LINK MINI VISION® Coronary Stent System)
- A drug coating (formulation of everolimus in a polymer coating)

Table 1 XIENCE V Stent System Product Description

	XIENCE V Rapid-Exchange (RX) EECSS	XIENCE V Over-the-Wire (OTW) EECSS
Available Stent Lengths (mm)	8, 12, 15, 18, 23, 28	8, 12, 15, 18, 23, 28
Available Stent Diameters (mm)	2.25*, 2.5, 2.75, 3.0, 3.5, 4.0	2.5, 2.75, 3.0, 3.5, 4.0
Stent Material	A medical grade L-605 Cobalt Chromium (CoCr) alloy MULTI-LINK VISION or	

	MULTI-LINK MINI VISION stent					
Drug Component	A conformal coating of a non-erodible polymer loaded with 100 μg/cm^2 of everolimus with a maximum nominal drug content of 181 μg on the largest stent (4.0 x 28 mm)					
Delivery System Working Length	143 cm			143 cm		
Delivery System Design	Single access port to inflation lumen. Guide wire exit notch is located 30 cm from tip. Designed for guide wires ≤ 0.014".			Sidearm adaptor provides access to balloon inflation/deflation lumen and guide wire lumen. Designed for guide wires ≤ 0.014".		
Stent Delivery System Balloon	A compliant, tapered balloon with two radiopaque markers to designate the stent placement on the balloon.					
Balloon Inflation Pressure	Nominal inflation pressure: 8 atm for the 2.25, 2.5 and 2.75 mm diameters; 9 atm for the 3.0, 3.5, and 4.0 mm diameters Rated Burst Pressure (RBP): 16 atm (1621 kPa) for all sizes					
Guiding Catheter Inner Diameter	≥ 5F (0.056")					
Catheter Shaft Outer Diameter (nominal)		2.25-3.0 mm	3.5-4.0 mm		2.5 mm	2.75 x 8 - 3.5 x 18 / 3.5 x 23 - 4.0 x 28
	Distal:	0.032"	0.035"	Distal:	0.032"	0.034" / 0.036"
	Proximal:	0.026"	0.026"	Proximal:	0.042"	0.042" / 0.042"

*The 2.25 mm diameter XIENCE V EECSS is only available on the RX platform.

A. Device Component Description

The XIENCE nano Stent System is a line extension to the currently approved XIENCE V Stent System, which was approved on July 2, 2008 (PMA P070015). The 2.25 mm diameter XIENCE V Stent System (XIENCE nano Stent System) is only available in the RX platform.

The device component is comprised of the balloon-expandable MULTI-LINK MINI VISION coronary stent pre-mounted onto the MULTI-LINK MINI VISION delivery system consisting of the Rapid Exchange (RX) platform. The MULTI-LINK MINI-VISION RX delivery systems were approved for deployment of the bare metal MULTI-LINK MINI-VISION stent in P020047/S003 (approved September 10, 2004).

The small XIENCE V stent design (2.25, 2.5, 2.75, and 3.0 mm diameters) is identical to the MULTI-LINK MINI VISION stent for the 2.0, 2.25, 2.5 mm diameters, and the MULTI-LINK VISION stent for the 2.75 mm and 3.0 mm diameter. All stent diameters will be available in 8-28 mm lengths.

B. Drug Component Description

Identical to the XIENCE V stent, the XIENCE nano stent is coated with everolimus (active ingredient), embedded in a non-erodible polymer (inactive ingredient).

B1. Everolimus

Everolimus is the active pharmaceutical ingredient in the XIENCE nano stent. It is a novel semi-synthetic macrolide immunosuppressant, synthesized by chemical modification of rapamycin (INN: sirolimus). The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin and the chemical structure is shown in Figure 1 below.

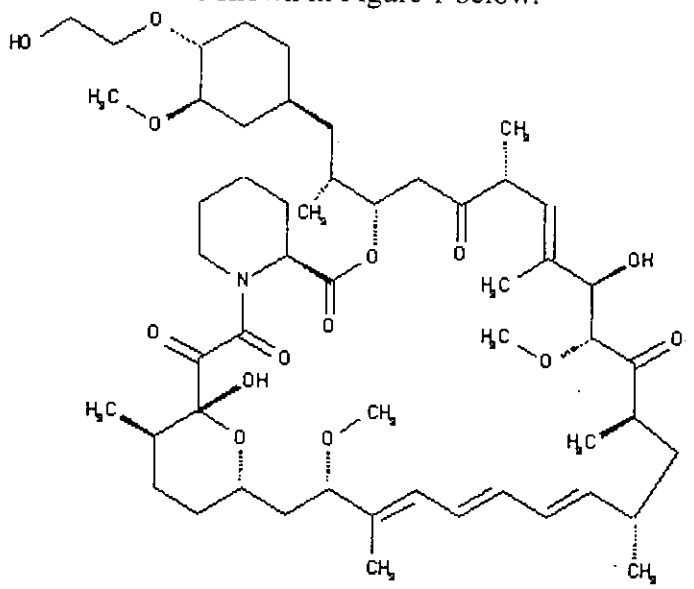


Figure 1 Chemical Structure of Everolimus

B2. Inactive Ingredients

The XIENCE nano stent contains inactive ingredients including poly n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus. PBMA is a homopolymer with a molecular weight of 264,000 to 376,000 dalton. PVDF-HFP is a non-erodible semi-crystalline random copolymer with a molecular weight of 254,000 to 293,000 dalton. The drug matrix copolymer is mixed with everolimus (83% /17% w/w polymer / everolimus ratio) and applied to the entire PBMA coated stent surface. The drug load is 100 $\mu g/cm^2$ for all product sizes. No topcoat layer is used. The chemical structure of the polymer components are shown in Figures 2a and 2b below.

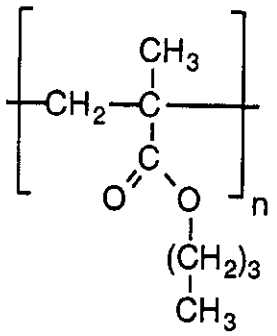


Figure 2a Chemical Structure of Poly (n-butyl methacrylate) (PBMA)

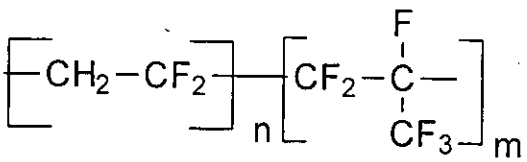


Figure 2b Formula for Poly(Vinylidene Fluoride-Co-Hexafluoropropylene) (PVDF-HFP)

The product matrix, including nominal dosages of everolimus in each XIENCE nano stent is described in Table 2. The nominal everolimus content is based on stent design and length.

Table 2 XIENCE nano Stent System Product Matrix and Everolimus Content

Model Number (RX)	Stent Diameter (mm)	Stent Length (mm)	Nominal Everolimus Content (µg)
1009544-08	2.25	8	37
1009544-12	2.25	12	56
1009544-15	2.25	15	75
1009544-18	2.25	18	88
1009544-23	2.25	23	113
1009544-28	2.25	28	132

C. Mechanism of Action

The mechanism by which the XIENCE nano stent inhibits neointimal growth as seen in pre-clinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell

proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 Rapamycin Associated Protein), also known as mTOR (mammalian Target Of Rapamycin), leading to inhibition of cell metabolism, growth and proliferation by arresting the cell cycle at the late G1 stage.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of patients with coronary artery disease including exercise, diet, drug therapy, percutaneous coronary interventions (i.e., balloon angioplasty, atherectomy, bare metal stents, coated stents, and other drug-eluting stents), and coronary artery bypass grafting (CABG) surgery. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The XIENCE nano Stent System is commercially available in the following countries:

Afghanistan	France	Mauritius	Suriname
Albania	French Polynesia	Morocco	Sweden
Algeria	French Guyana	Myanmar	Switzerland
Argentina	Georgia	Netherlands	Syria
Aruba	Germany	New Caledonia	Taiwan
Australia	Greece	New Zealand	Thailand
Austria	Guadeloupe	Nicaragua	Trinidad,Tobago
Bahamas	Guatemala	Niederl.Antill.	Tunisia
Bahrain	Guyana	Nigeria	Turkey
Bangladesh	Honduras	Norway	Uganda
Barbados	Hong Kong	Oman	Ukraine
Belarus	Hungary	Pakistan	United Arab Emirates
Belgium	Iceland	Panama	United Kingdom
Belize	India	Paraguay	Uruguay
Bermuda	Indonesia	Peru	Uzbekistan
Bolivia	Iran	Philippines	Venezuela
Brazil	Iraq	Poland	Vietnam
BritishVirgin Islands	Ireland	Portugal	Zimbabwe
Brunei	Israel	Qatar	
Bulgaria	Italy	Republic of Armenia	
Cambodia	Jamaica	Republic of Yemen	
Canada[1]	Jordan	Reunion	
Cayman Islands	Kenya	Romania	
Chile	Kosovo	Russian Fed.	
China	Kuwait	San Marino	
Colombia	Latvia	Saudi Arabia	
Costa Rica	Lebanon	Serbia	
Cyprus	Libya	Singapore	
Czech Republic	Liechtenstein	Slovakia	
Denmark	Lithuania	Slovenia	
Dominican Republic	Luxembourg	South Africa[2]	
Egypt	Macedonia	South Korea	
El Salvador	Malaysia	South Yemen	
Estonia	Malta	Spain	
Finland	Martinique	Sri Lanka	

[1] XIENCE V 2.25mm stent is available under Special Access scheme in Canada

[2] XIENCE V (including 2.25 mm) is available under Section 21 approval

As of August 31, 2010, 79,131 XIENCE nano (2.25 mm) Stent Systems have been distributed outside the United States. The XIENCE nano Stent System has not been withdrawn from marketing in any country for any reason.

VIII. SUMMARY OF PRECLINICAL STUDIES

A series of non-clinical laboratory studies related to the XIENCE nano product were performed. Studies included those performed on the bare metal stent system (MULTI-LINK VISION or MULTI-LINK MINI VISION stent mounted on the stent delivery system), the coated stent alone, the polymer-only coated stent alone (the MULTI-LINK VISION or MULTI-LINK MINI VISION with the PBMA primer layer and PVDF-HFP polymer layer), or the finished combination product (XIENCE nano Stent System).

A1. Biocompatibility Testing

The biocompatibility testing information included in the original PMA submission (P070015, approved July 2, 2008) is directly applicable to this PMA supplement. Please refer to the original SSED for details regarding the biocompatibility studies.

The complement activation study is being leveraged from the testing conducted on a stent system with identical stent material, drug coating formulation, drug dose density, sterilization cycle and packaging components. This additional biocompatibility study for complement activation was performed to augment the hemocompatibility studies of XIENCE V Stent System provided in PMA P070015. The outcomes of the biocompatibility tests provide passing results.

A2. *In Vitro* Engineering Testing

The *in vitro* engineering testing included in the original PMA submission (P070015, approved July 2, 2008) is directly applicable to this PMA supplement. Based on the similarities in design, test results were leveraged from the MULTI-LINK VISION and MINI VISION Coronary Stent System (CSS), or XIENCE V Stent System testing provided in PMA P070015. The *in vitro* bench testing plan to support commercial approval of the XIENCE nano Stent System was re-evaluated in light of the release of US FDA April 18, 2010 *"Guidance for Industry and FDA Staff - Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems,"* which superseded the previous guidance document. Therefore, only the testing information specific to the XIENCE nano (2.25 mm diameter) stent is summarized below in Table 3. "Pass" denotes that the test results met product specifications and/or the recommendation in the guidance documents.

Table 3 ***In Vitro*** **Engineering Studies**

Test	Test Description	Results
Material Characterization Testing		
Corrosion Testing	The initial pitting corrosion testing conducted on the MULTI-LINK VISION stents (P020047) is leveraged to support the approval of the XIENCE nano Stent System.	PASS
Fretting Corrosion	Evaluates the presence of fretting corrosion on the stent after ten year accelerated fatigue testing (400 million cycles) in an overlapped configuration on a 15 mm static bend. The test conducted for the small XIENCE V stent is leveraged for the XIENCE nano stent due to the identical material, design, and manufacturing process. No evidence of fretting corrosion was found. The results met all acceptance criteria.	PASS
Stent Dimensional and Functional Attributes		
Stent Percent Surface Area	Determines the metal to artery ratio by dividing the abluminal stent surface area by the theoretical cylindrical stented vessel area. It is a theoretical calculation based upon a 3D computational solid model of the stent design. The calculated value for the XIENCE nano at the nominal 2.25 mm diameter is 15%.	Descriptive Only
Stent Uniformity of Expansion Test	Determines the uniformity of expansion along the stent length. The XIENCE nano units were inflated to either nominal or post-dilated inner diameters, deflated, and diameter measurements were taken at various points along the stent length. Measurements were averaged and all XIENCE nano stents met product specifications.	PASS
Stent Percent Length Change (Foreshortening) Test	Determines the difference in stent length pre-and post-expansion to either nominal or post-dilated inner diameters. All XIENCE nano stents met product specifications.	PASS
Stent Percent Recoil Test	Quantifies the amount of recoil of the stent after balloon expansion. The system was inflated to either nominal or post-dilated diameters and measurements were taken of the stent diameter at various locations along the stent length. The system was then deflated and the same measurements taken. The percent recoil is calculated by subtracting the average stent inner diameter (ID) without the balloon from the average stent ID with the balloon, dividing by the average stent ID with the balloon and multiplying by 100. All XIENCE nano stents met product specifications.	PASS
Radial Stiffness	Radial stiffness was evaluated on the XIENCE nano stent as a characterization test.	For characterization only
Stent Radial (Hoop) Strength Test	Testing was conducted to determine the radial strength of the stent under compression force. Stents were expanded to either nominal or post-dilated diameters, placed in an Instron tester, and subjected to incrementally increasing compression forces. The pressure at which deformation is no longer completely reversible was recorded. All XIENCE nano stents met product specifications.	PASS
Finite Element Analysis (FEA)	The XIENCE nano stent has identical stent designs, material properties, maximum expansion diameters, and fatigue loading steps, fatigue safety factors as that of the small XIENCE V stents and hence the in-depth FEA analysis conducted on the XIENCE V stent (P070015) can be leveraged in support of the XIENCE nano stent. The testing indicates adequate margins of safety for the XIENCE nano stent. A supplemental FEA was also performed at nominal expansion diameter of 2.25 mm to verify the worst-case expansion diameter for stress/strain and fatigue safety for XIENCE nano. The analysis	PASS

Test	Test Description	Results
	simulated overlapped stent deployment and incorporated a bending radius of 15 mm and verified that the worst case for stress/strain as well as the lowest fatigue safety factor occurs at maximum post-dilation (3.5 mm) and not at nominal expansion of 2.25 mm. The supplemental FEA, therefore, confirmed that the FEA testing submitted for the XIENCE V stent can be appropriately leveraged to verify the short and long term structural behavior of the XIENCE nano stent under worst-case deployment conditions. Results of the FEA were used to determine the worst-case test size to be evaluated in accelerated durability testing and chronic coating particulates. Based upon these results testing can be leveraged from the XIENCE V stent for both accelerated durability testing and chronic coating particulates.	
Magnetic Resonance Imaging (MRI)	The initial MRI test results for the XIENCE V Stent System were leveraged to support the approval of the XIENCE nano Stent System. In addition to the leveraged testing, supplemental information and calculations support MR Conditional labeling for the XIENCE nano and XIENCE V Stent Systems under MR imaging at 1.5 T and 3 T and at lengths up to 68 mm for a whole body averaged SAR of 2 W/kg (normal operating conditions) at spatial gradients up to 2500 G/cm. The conservative maximum temperature rise cited in the labeling for these conditions will be 3°C, with no cooling effects from perfusion or blood flow.	PASS
Delivery System Dimensional and Functional Attributes		
Catheter Dimensional Measurements	The following characteristics were tested to conform to the applicable specifications: Tip Length, Tip Seal Length, Tip Unsealed Length, Proximal Unsealed Balloon Shaft, Total Catheter Length & Distal Catheter Length, Guide Wire Lumen Dimensions (Tip Inner Diameter (ID) & Distal Shaft Junction Notch ID), Stent Placement, Balloon Shoulder to Marker Alignment, Balloon Working Length, Proximal Shaft Marker Locations (Femoral Marker & Brachial Marker), Delivery System Outer Diameters (Distal Shaft OD, Mid Shaft OD, Proximal Shaft OD, Tip Entry OD, Guide Wire Notch OD). All XIENCE nano Stent Systems met product specifications.	PASS
Delivery, Deployment, and Retraction	The delivery, deployment and retraction evaluated for system deliverability, balloon marker placement, stent radiopacity, system pullback out of deployed stent and into the guide catheter, and compatibility with accessory devices. Testing demonstrated that the stent system could be delivered to the target location, deployed, and retracted, thus meeting required product specifications.	PASS
Balloon Rated Burst Pressure	Statistically demonstrates with 95% confidence, at least 99.9% of the XIENCE nano Stent Systems will not rupture below the rated burst pressure (RBP) and to demonstrate that at a 95% confidence level, at least 99% of the XIENCE nano Stent Systems will not rupture below the maximum labeled compliance (MLC) pressure. All systems met product specifications and confidence/reliability limits.	PASS
Unconstrained Balloon Fatigue	Statistically demonstrates with 95% confidence, at least 90% of the XIENCE nano Stent Systems will sustain 10 repeated inflations to the rated burst pressure inside the stent. All XIENCE nano Stent Systems met product specifications.	PASS
Stent Diameter vs. Balloon Pressure	Determines how the diameter of a deployed balloon varies with applied balloon pressures. All XIENCE nano Stent Systems met	PASS

Test	Test Description	Results
(Compliance)	product specifications.	
Soft Tip Tensile	Determines the tensile strength of the soft tip. All XIENCE nano Stent Systems met product specifications.	PASS
Distal Delivery System Tensile	Determines the tensile strength of the distal portion of the delivery system. All XIENCE nano Stent Systems met product specifications.	PASS
Proximal Adaptation Tensile Strength	Determines the tensile strength of the proximal adaptation of the delivery system. All XIENCE nano Stent Systems met product specifications.	PASS
Delivery System Crossing Profile – Crimped Stent Outer Diameter	Determines the crimped stent outer diameter. Measurements were taken at various locations along the length of the stent and averaged to calculate the mean outer diameter. All XIENCE nano Stent Systems met product specifications.	PASS
Delivery System Balloon Inflation/Deflation Times	Determines the amount of time required to inflate or deflate the delivery catheter balloon. Inflation times were tested for information only. All XIENCE nano Stent Systems met product specifications for deflation times.	PASS
Stent Dislodgement	Determines the amount of force required to displace a stent in both the distal and proximal direction from its original, crimped position on the delivery system balloon after a pre-conditioning step where the system is tracked through a tortuous artery model. All XIENCE nano Stent Systems met product specifications.	PASS
Delivery System Guiding Catheter Pullback	Statistically demonstrates that with 95% confidence, at least 99% of the XIENCE nano Stent Systems can be successfully retracted back into a 5F guiding catheter after tracking through a simulated tortuous model prior to the deployment of the stent. All systems met product specifications and confidence/reliability limits.	PASS
Delivery System Preparation	Evaluates the ease of preparing the XIENCE nano Stent System using the aspiration method. All XIENCE nano Stent Systems met product specifications.	PASS
Delivery System Inner Member Collapse	Verifies that irreversible collapse of the inner member does not occur at or below 300 psi. All XIENCE nano Stent Systems met product specifications.	PASS
Catheter Kink and Flexibility Test	Determines the radius of curvature at which the delivery system kinks. All XIENCE nano Stent Systems met product specifications.	PASS
Catheter Torque Test - Turns to Failure	Determines the minimum number of rotations to break joints and/or materials or to lose functional integrity of the delivery system. All XIENCE nano Stent Systems met product specifications.	PASS

A3. Coating Characterization Testing

The coating characterization testing included in the original PMA submission (P070015, approved July 2, 2008) is directly applicable to this PMA supplement. Therefore, only the testing information specific to the XIENCE nano (2.25 mm diameter) stent is summarized below in Table 4. "Pass" denotes that the test results met product specifications and/or the recommendation in the guidance documents.

Table 4 Coating Characterization Testing

Test	Test Description	Results

Test	Test Description	Results
Stent Coating Durability		
Coating Surface Integrity	Determines the stent coating surface integrity of the XIENCE nano stent after tracking through a tortuosity fixture, expansion, and post-dilated to RBP. Defect quantities and sizes were recorded. The compromised coating area was calculated as a percentage of entire coated stent surface. All stents met product specifications.	PASS
Particulate - Beaker Method (Over-expansion)	Determines the particulate matter generated during deployment and over expansion of the XIENCE nano stent in a beaker of water. The distal end (balloon and stent) was inserted into glassware filled with clean water. The stents were deployed and post-dilated to the maximum stent diameter. After agitation, aliquots of the water were withdrawn and the particles quantities and sizes were counted and recorded. All stents met product specifications.	PASS
Particulate - Tracking Method (Simulated Use)	Determines the particulate matter after navigating simulated, challenging vasculature followed by deployment. The XIENCE nano system was tracked through a simulated tortuous artery model and the stent was deployed unconstrained to RBP inside the simulated vasculature. Water was drawn through the vasculature and the particle quantities and sizes were counted and recorded. All stents met product specifications.	PASS

A4. Chemistry, Manufacturing, & Controls (CMC) Testing

The CMC information included in the original PMA submission (P070015, approved July 2, 2008) is directly applicable to this PMA Supplement; therefore the information is not repeated herein.

A5. Stability/ Shelf Life

A formal stability study was conducted to establish a shelf life / expiration date for the XIENCE nano Stent System. Testing included appearance, total content, drug release, degradation products, oxygen content, molecular weight and polydispersity, microbial challenge (packaging integrity) and endotoxin (pyrogen), particulates and butylated hydroxytoluene (BHT) content. Testing to establish container closure integrity was conducted to ensure sterility was maintained during the shelf life of the product. Functional testing of the stent system was conducted on aged product. The data generated to-date support a shelf life of 1 year.

A6. Sterilization

The XIENCE nano Stent System is sterilized using ethylene oxide (EtO) sterilization. The sterilization parameters used to sterilize XIENCE nano are identical to the parameters used to sterilize XIENCE V. The cycle is validated per the ISO 11135-1: 2007 Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization.

Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10-6. In addition, the amount of bacterial endotoxins was verified to be within the specification limits.

A7. Animal Studies

The *in vivo* animal studies included in the original PMA submission (P070015, approved July 2, 2008) are directly applicable to this PMA Supplement; therefore, the information is not repeated herein.

IX. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the XIENCE V stent.

Adverse events (in alphabetical order) which may be associated with coronary stent use in native coronary arteries include, but are not limited to:

Abrupt closure
Access site pain, hematoma or hemorrhage
Acute myocardial infarction
Allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers; and drug reactions to antiplatelet drugs or contrast agent
Aneurysm
Arterial perforation and injury to the coronary artery
Arterial rupture
Arteriovenous fistula
Arrhythmias, atrial and ventricular
Bleeding complications, which may require transfusion
Cardiac tamponade
Coronary artery spasm
Coronary or stent embolism
Coronary or stent thrombosis
Death
Dissection of the coronary artery
Distal emboli (air, tissue or thrombotic)
Emergent or non-emergent coronary artery bypass graft surgery
Fever
Hypotension and/or hypertension
Infection and pain at insertion site
Injury to the coronary artery
Ischemia (myocardial)
Myocardial infarction (MI)
Nausea and vomiting

Palpitations
Peripheral ischemia (due to vascular injury)
Pseudoaneurysm
Renal failure
Restenosis of the stented segment of the artery
Shock/pulmonary edema
Stroke/cerebrovascular accident (CVA)
Total occlusion of coronary artery
Unstable or stable angina pectoris
Vascular complications including at the entry site which may require vessel repair
Vessel dissection

Zortress®, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prophylaxis of organ rejection in adult kidney transplant recipients at low-moderate immunologic risk, at the dose of 1.5 mg/day. Outside the United States, Zortress® is sold under the brand name Certican® in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor® for the treatment of patients with advanced renal cell carcinoma (cancer) after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The following list includes the known risks of everolimus at the oral doses indicated above:

- Abdominal pain (including upper abdominal pain)
- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation
- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dyspnea
- Dysgeusia
- Dyspepsia
- Dysuria
- Dry skin
- Edema (peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia (may include new onset of diabetes)
- Hyperlipidemia
- Hyperkalemia

- Hypertension
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections)
- Insomnia
- Interaction with strong inhibitors and inducers of CY3PA4
- Leukopenia
- Lymphoma and other malignancies (including skin cancer)
- Male infertility (azospermia and/or oligospermia)
- Mucosal inflammation (including oral ulceration and oral mucositis)
- Nausea
- Neutropenia
- Non-infectious pneumonitis
- Pain: extremity, incision site and procedural, and back
- Proteinuria
- Pruritus
- Pyrexia
- Rash
- Stomatitis
- Thrombocytopenia
- Thrombotic microangiopathy (TMA)/Thrombotic thrombocytopenic purpura (TTP)/ Hemolytic uremic syndrome (HUS)
- Tremor
- Urinary tract infection
- Upper respiratory tract infection
- Vomiting

Live vaccines should be avoided and close contact with those that have had live vaccines should be avoided. Fetal harm can occur when administered to a pregnant woman. There may be other potential adverse events that are unforeseen at this time.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The XIENCE nano safety and effectiveness information is derived from the SPIRIT Small Vessel Registry (SPIRIT SV trial). The SPIRIT SV trial evaluated the safety and efficacy of the XIENCE nano Stent System in improving coronary luminal diameter in subjects with symptomatic heart disease due to a maximum of two de novo native coronary artery lesions in small vessels (≥ 2.25 mm to < 2.50 mm), each in a different epicardial vessel. Follow-up through 1 year is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

A. Study Design

The SPIRIT SV trial is a prospective, single-arm, open-label, US multicenter registry study using XIENCE nano Stent System with stent diameter of 2.25 mm. The trial enrolled a total of 150 subjects at 33 sites. The first 69 enrolled subjects who received the XIENCE nano stent were assigned to the angiographic cohort. The clinical trial design for SPIRIT SV is summarized in Table 5 below.

The SPIRIT SV trial follow-up included office visits at 30 ± 7 days, 240 ± 28 days, and at 1 year ± 28 days. An office visit or telephone follow-up is required annually for years 2 through 5. An ECG was performed for all subjects at the 30-day visit, 240-day visit, and 1-year visit. Angiographic follow-up was also required at the 240-day visit for the angiographic cohort. The primary endpoint of the SPIRIT SV trial was target lesion failure (TLF) at 1 year. TLF is a composite endpoint of cardiac death, target vessel MI and clinically indicated Target Lesion Revascularization (CI-TLR).

Subjects enrolled in the trial had: 1) one target lesion (treated with one XIENCE nano stent), 2) two target lesions (treated with two XIENCE nano stents), or 3) one target lesion (treated with one XIENCE nano stent) and one non-target lesion (treated with a commercial size of the XIENCE V Stent System). Planned overlap was allowed for both the target and non-target lesions, but only with a commercial size of the XIENCE V Stent System. Bailout was allowed with a commercial XIENCE V stent or the XIENCE nano stent. A total of 69 subjects were enrolled in the angiographic cohort.

The primary analysis of the SPIRIT SV data was performed on the Full Analysis Set (FAS) population which was defined as the subjects who received the XIENCE nano stent. The Intent to Treat (ITT) population was defined as the subjects enrolled into the study, regardless of the treatment actually received; this population excludes de-registered subjects.

Table 5 SPIRIT Small Vessel Trial Design

	SPIRIT Small Vessel
Study Type/Design	• Multi-center • Non-randomized • Open-label • Non-blinded • Single-arm
Number of Subjects Enrolled	Total : 150
Treatment	Up to two *de novo* lesions in different epicardial vessels
Lesion Size	RVD: ≥ 2.25 < 2.50 mm Length: ≤ 28 mm
Stent Sizes (XIENCE nano)	Diameter: 2.25 mm Length: 8, 18, 28 mm
Post-procedure Antiplatelet Therapy	Clopidogrel 12 months minimum (or ticlopidine per site standard), aspirin indefinitely
Primary Endpoint	Target lesion failure (TLF) at 1-year (composite of cardiac death, target vessel MI and clinically-indicated TLR)
Co-Primary Endpoint	None
Major Secondary Endpoint	None
Clinical Follow-up	30, 240, days, 1 to 5 years
Angiographic Follow-up	240 days (n = 69)
Status	One year reported

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the SPIRIT SV trial was limited to subjects who met the eligibility criteria and who provided a signed informed consent form prior to enrollment. Subjects had to be at least 18 years old, with evidence of myocardial ischemia based on the presence of angina, silent ischemia, a positive functional study or reversible ECG changes consistent with ischemia. Female subjects with childbearing potential had to have a negative pregnancy test within 7 days of the index procedure.

The key angiographic inclusion criteria applied to the target and non-target lesion are listed below:

- *De novo* lesions in native coronary arteries (Target lesion: RVD ≥ 2.25 mm to < 2.50 mm; Non-target lesion: RVD ≥ 2.5 mm to ≤ 4.25 mm; lesion length ≤ 28 mm) with one lesion in one vessel or two lesions in two separate epicardial vessels.
- If two target lesions or one target and one non-target lesion, both lesions must have satisfied the angiographic eligibility criteria of %DS of ≥ 50% and < 100% with a TIMI flow of ≥ 1.

The key angiographic exclusion criteria applied to the target and non-target lesion are listed below:

- Location in an arterial or vein graft
- Aorto-ostial location

- Left main location
- Lesion located within 2 mm of the origin of the LAD and LCX
- Extreme angulation (≥ 90°) or excessive tortuosity (≥ two 45° angles) proximal to or within the target or non-target lesion
- Heavy calcification proximal to or within the target or non-target lesion
- Target or non-target vessel contain thrombus
- Another clinically significant lesion located in the same epicardial vessel as the target or non-target lesion
- Target or non-target vessel has been previously treated with any type of PCI < 9 months prior to index procedure
- Vessel not intended to be treated with the XIENCE nano Stent System or commercial XIENCE V Stent System has been previously treated with any type of PCI < 90 days prior to index procedure.
- Clinically significant lesions in any vessel or side branch that may require PCI ≤ 90 days after the index procedure are also excluded.

2. Follow-up Schedule

All subjects will be followed for a five-year period. All subjects were required to have an office follow-up visit at 30 days, 240 days, and at 1 year. Annual office or telephone follow-up visits are required at years 2 through 5.

3. Stent Thrombosis Definitions

Stent Thrombosis was defined in the protocol as clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis (thrombus within or adjacent to the treated target lesion), or in the absence of angiography, any unexplained death (at any time following the index procedure) or acute MI in the distribution of the target lesion within 30 days of the index procedure. Stent thrombosis was categorized as acute (≤ 1 day), subacute (> 1 day to ≤ 30 days), or late (> 30 days) relative to the index procedure.

Stent thrombosis was defined by ARC criteria:
Timing:

- Acute ST: 0 to 24 hours post stent implantation
- Subacute ST: >24 hours - 30 days post stent implantation
- Late ST: 30 days to 1 year post stent implantation
- Very late ST: > 1 year post stent implantation

Level of probability:

- Definite ST - considered to have occurred by either angiographic (with at least one of the following: acute onset of ischemic symptoms at rest; new ischemic changes suggestive of acute ischemia; or a typical rise and fall of cardiac biomarkers) or pathologic confirmation.
- Probable ST - considered to have occurred after intracoronary stenting in the following cases:

1. Any unexplained death within the first 30 days.
2. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.

- Possible ST - considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up.[3]

4. Clinical Endpoints

The primary endpoint of the SPIRIT SV was target lesion failure (TLF) at 1 year. TLF was defined as the composite endpoint of Cardiac Death, Target Vessel Myocardial Infarction (Q-wave and non-Q-wave), and clinically-indicated Target Lesion Revascularization (CI-TLR) by Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI).

Other key secondary endpoints to examine the safety and efficacy included the following:

- Acute Success: (Combined clinical/angiographic)
- Clinical Device Success[4] (Per lesion basis, for target lesions treated by the XIENCE nano Stent with or without planned overlap)
- Clinical Procedural Success[5] (Per subject basis, for all target and non-target lesions)
- Clinical Endpoint in hospital and at each follow-up point (30 days, 240 days, 1, 2, 3, 4 and 5 years) (for ALL lesions)
- Component Endpoints (each evaluated per protocol definition and ARC definition)

  All Death (cardiac, vascular, non-cardiovascular)
  Target Vessel MI - Q-wave and non Q-wave (defined as MI not clearly attributable to a non-target vessel)
  Non Target Vessel MI (Q-wave, Non Q-wave)
  CI-TLR
  Clinically indicated Target Vessel Revascularization (TVR = TLR and non-TLR in TV)

[3] All stent thrombosis data presented reflect definite + probable stent thrombosis only.
[4] Clinical Device Success was defined as the successful delivery and deployment of the first study stent intended to be implanted at the intended target lesion (or in the overlapping stent setting, a successful delivery and deployment of the intended first and second investigational stents) and successful withdrawal of the stent delivery system with attainment of final residual stenosis of <50% of the target lesion by QCA (or by visual estimation if QCA unavailable). Bailout lesions were included as device success only if the above criteria for clinical device success were met for the bailout stent.
[5] Clinical Procedural Success was defined as the achievement of a final in-stent diameter stenosis (DS) of <50% (by QCA) using the assigned device and with any adjunctive devices, without the occurrence of cardiac death, target vessel MI (per protocol definition), or repeat coronary revascularization of the target lesion during the hospital stay (up to 7 days if a subject is still in the hospital). If QCA %DS was not available, procedure success data were considered missing.

All TLR (CI and non-CI)
All TVR (CI and non-CI)
All Coronary Revascularization (TVR and non-TVR)

- Composite Endpoints
  Cardiac Death/MI
  Cardiac Death/All MI/CI-TLR
  All Death/All MI/All Coronary Revascularization
- Stent Thrombosis (to be evaluated per protocol definition and ARC)
  By Timing (Acute, Subacute, Late and Very late)
  By Evidence (Definite, Probable and Possible)
- Angiographic Endpoints at 240 days (for target lesions of the angiographic cohort)
  In-segment, in-stent, proximal and distal LL
  In-segment, in-stent, proximal and distal % diameter stenosis (%DS)
  In-segment, in-stent, proximal and distal angiographic binary restenosis (ABR) rate

B. Accountability of PMA Cohort

There were a total of 150 subjects enrolled in SPIRIT SV trial at 33 US sites which included a total of 69 investigators. The FAS population (primary analysis population) consisted of 144 subjects as 6 subjects did not receive the XIENCE nano stent. Subjects in the trial were terminated if a subject withdrew consent, the physician withdrew the subject, the subject was lost to follow-up or the subject died. In the FAS population, 3.5% (5/144) of subjects were considered terminated from the study on or prior to the 30-day follow-up, 4.9% (7/144) of subjects were terminated on or prior to the 240-day follow-up. In the angiographic cohort 5.8% (4/69) of subjects were terminated on or prior to the 240-day follow-up. In the FAS population, 6.9% (10/144) of subjects were terminated on or prior to the 1-year follow-up.

C. Study Population Demographics and Baseline Parameters

In the FAS population, the mean age was 62.97 ± 10.59 years and 61.8% (89/144) were male. In subjects treated with the XIENCE nano Stent System, 22.9% (32/140) were tobacco users, 81.9% (118/144) were hypertensive requiring medication, 86.5% (122/141) had hypercholesterolemia requiring medication, and 39.2% (56/143) were diabetic. Additionally, 68.8% (99/144) of the subjects had stable angina and 27.1% (39/144) had unstable angina. A prior cardiac intervention at the target vessel had occurred in 20.6% (29/141) of subjects, while 27.5% (39/142) of subjects had a prior MI, and 54.2% (65/120) had a family history of premature coronary artery disease.

In the FAS population, LAD coronary artery treatment was performed in 40.7% (59/145) of lesions, LCX/ramus treatment in 31.0% (45/145), and RCA treatment in 28.3% (41/145). In the FAS population, the incidence of calcified or eccentric target lesions were 9.0% (13/144) and 10.4% (15/144), respectively. TIMI 3 flow was

present in 92.4% (134/145) of target lesions. In the FAS population, the frequency of type B1 or type B2 target lesions (according to ACC/AHA classification) was 47.6% (69/145) and 23.4% (34/145), respectively. In the FAS population the mean pre-procedure lesion length was 13.38 ± 5.31 mm, pre-procedure RVD 2.13 ± 0.23 mm, pre-procedure MLD 0.55 ± 0.20 mm, and pre-procedure %DS 72.84 ± 9.26.

D. Safety and Effectiveness Results

The results are presented in Table 6 (Primary endpoint), Table 7 (Clinical Results) Table 8 (Stent Thrombosis Results), Table 9 (Angiographic Results), and Figure 3 (TLF Free Survival). These analyses are based on the FAS population.

In the FAS population, the 1-year TLF rate was 8.1% for which the upper limit of the one-sided 95% confidence interval was 13.03%, which met the pre-specified performance goal of 20.4% ($p<0.0001$).

Table 6 SPIRIT Small Vessel Primary Endpoint Results

Primary Endpoint	XIENCE nano (N=144)	Upper 1-Sided 95% CL	P-Value[1]
1 Year TLF	8.1% (11/136)	13.03%	<0.0001

Notes:
- N is the total number of subjects.
- TLF includes cardiac death, target vessel MI (per protocol definition) and clinically-indicated TLR.
- Time Frame includes follow-up window (365 + 28 days).

[1] One-sided p-value by testing against the performance goal of 20.4% using exact test at 0.05 significance level.

Table 7 SPIRIT Small Vessel Registry Clinical Endpoint Results through 1 Year

XIENCE nano	Per Protocol Definition
ACUTE SUCCESS	**ITT* (N = 149)**
Clinical Device Success	95.21% (139/146)
Clinical Procedure Success	97.93% (142/145)
CLINICAL ENDPOINTS	**FAS (N = 144)**
Component Endpoints	
All Death	1.5% (2/136)
Cardiac Death	1.5% (2/136)
Non-Cardiac Death	0.0% (0/136)
Target Vessel MI	1.5% (2/136)
Non Target Vessel MI	0.0% (0/136)
Clinically-Indicated TLR (CI-TLR)	5.1% (7/136)
Clinically-Indicated TVR (CI-TVR)	8.8% (12/136)
All TLR	6.6% (9/136)
All TVR	10.3% (14/136)
All Revascularization	14.7% (20/136)
Composite Endpoints	
Cardiac Death or MI	2.9% (4/136)
Cardiac Death or All MI or CI-TLR	8.1% (11/136)
All Death or All MI or All Revascularization	16.9% (23/136)

Notes:
- N is the total number of subjects; L is the number of lesions.
- Per protocol MI definition was used for Target Vessel MI, Non Target Vessel MI and all composite endpoints.
- Time Frame includes follow-up window (365 ± 28 days).
- Non Target Vessel MI includes MI not attributed to the treated vessel.
- All Revascularization includes TVR and non-TVR, and non-treated vessel revascularization.

* The ITT population provides the most accurate estimate of successful XIENCE nano stent implantation because it includes all subjects regardless of whether the attempted implantation of XIENCE nano stent was successful.

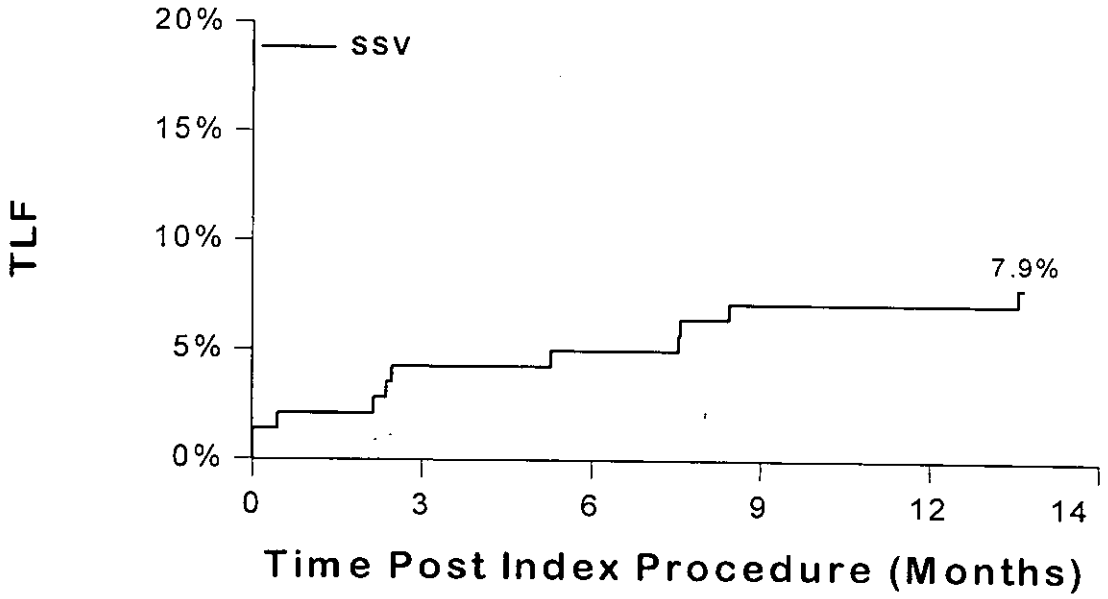
Table 8 SPIRIT Small Vessel Stent Thrombosis Results through 1 Year

XIENCE nano	FAS (N = 144)	
Stent Thrombosis	**Per Protocol Definition**	**Per ARC Definition (Definite + Probable)**
Acute (≤ 1 day)	0.0% (0/143)	0.0% (0/143)
Subacute (>1 – 30 days)	0.7% (1/140)	0.7% (1/140)
Acute/Subacute (0 – 30 days)	0.7% (1/140)	0.7% (1/140)
Late (31 – 393 days)	1.5% (2/135)	0.7% (1/135)
Overall (0 – 393 days)	2.2% (3/136)	1.5% (2/136)

Table 9 SPIRIT Small Vessel 240-Day Angiographic Results (Angiographic Cohort[1])

XIENCE nano	FAS (N = 69) (L = 69)
240-day Late Loss (mm)	
In-Stent	0.20 ± 0.40 (52)
In-Segment	0.16 ± 0.41 (52)
Proximal	0.21 ± 0.35 (34)
Distal	0.00 ± 0.28 (45)
240-day % Diameter Stenosis	
In-Stent	12.86 ± 19.58 (52)
In-Segment	20.85 ± 22.53 (52)
Proximal	14.31 ± 13.16 (37)
Distal	10.40 ± 8.45 (46)
240-day Angiographic Binary Restenosis	
In-Stent	3.8% (2/52)
In-Segment	9.6% (5/52)
Proximal	2.7% (1/37)
Distal	0.0% (0/46)

Notes:
N is the total number of subjects. L is the total number of lesions.
[1] Per Protocol defined qualifying angiogram with follow-up window extended to 268 days.
240-day angiographic data is only available for 52 subjects.



TLF	Event Free	Event Rate
XIENCE nano	92.1%	7.9%

Note:
- Time Frame includes follow-up window (365 + 28 days).

Figure 3 **SPIRIT Small Vessel Registry: Kaplan Meier Time-to-Event Curve for TLF through 1 Year**

Gender-Based Analysis

Cardiovascular disease is the leading cause of death for both women and men in the U.S. and coronary artery disease is a major cause of morbidity and mortality in women. It is estimated that the prevalence of coronary artery disease in the United States is 9.1% (9,200,000) in males and 7.0% (8,400,000) in females for adults at least 20 years old according to the American Heart Association 2010 Update.[6] However, it is estimated that only 36% of annual PCIs are performed in women.[7] In PCI clinical trials, women represent only 25-35% of the enrolled populations, and there are relatively little gender-specific data. The disproportionate enrollment distribution in these trials may be partly attributable to gender differences in symptoms and pathophysiology,[8] which may lead to under-diagnosis and under-referral of female patients with CAD. Women tend to have

[6] Lloyd-Jones D, Adams R, Carnethon M, De Simone G, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; 121:e46-215.
[7] Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; 119(3):e21-181.
[8] Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights From the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: Gender Differences in Traditional and Novel Risk Factors, Symptom Evaluation, and Gender-Optimized Diagnostic Strategies. J Am Coll Cardiol 2006 47: S4-20.

worse clinical outcomes compared to men, most likely due to a higher baseline risk profile and more complex angiographic characteristics.[9,10,11]
The applicant also performed a post-hoc multivariable gender analysis of the SPIRIT Small Vessel clinical trial. However, it should be noted that the SPIRIT SV trial was not powered to detect any differences between genders, and a subgroup analysis was not pre-specified in the Statistical Analysis Plan. Therefore, due to the limited sample size and the small number of events, the results from the analysis below should be considered exploratory without definitive conclusions.

The baseline SPIRIT SV trial subject characteristics stratified by gender are shown in Table 10. Compared to the men, women were more likely to be diabetics treated with insulin [27.3% (15/55) for females versus 8.0% (7/88) for males], and less likely to be smokers [13.0% (7/54) smokers for females versus 29.1% (25/86) smokers for males]. In terms of baseline angiographic characteristics, the differences in lesion length and pre-procedure RVD, MLD, or %DS were not found to differ significantly between females and males in this post-hoc analysis.

Table 10: Demographics, Risk Factors, and Baseline Angiographic Characteristics for All Female and All Male Subgroups in the SPIRIT SV Clinical Trial

Subject Characteristics	Females (N=55) (M=55)	Males (N=89) (M=90)	P Value
Baseline Demographics, Mean ± SD (n)			
Age (year)	64.74 ± 11.28 (55)	61.88 ± 10.05 (89)	0.1260
Baseline Risk Factors, % (No./total)			
All Diabetes	49.1% (27/55)	33.0% (29/88)	0.0778
Diabetes Treated with Insulin	27.3% (15/55)	8.0% (7/88)	0.0034
Current Tobacco Use	13.0% (7/54)	29.1% (25/86)	0.0378
Hypertension Requiring Medication	83.6% (46/55)	80.9% (72/89)	0.8243
Hypercholesterolemia Requiring Medication	85.2% (46/54)	87.4% (76/87)	0.8012
Stable Angina	72.7% (40/55)	66.3% (59/89)	0.4632
Unstable Angina	25.5% (14/55)	28.1% (25/89)	0.8474
Prior MI	20.4% (11/54)	31.8% (28/88)	0.1759
Target Vessel, % (No./total)			
LAD	45.5% (25/55)	37.8% (34/90)	0.3876
Circumflex or Ramus	30.9% (17/55)	31.1% (28/90)	1.0000
RCA	23.6% (13/55)	31.1% (28/90)	0.3502
LMCA	0.0% (0/55)	0.0% (0/90)	N/A
Pre-Procedure QCA Analysis, Mean ± SD (m)			
Lesion Length (mm)	13.62 ± 5.81 (55)	13.23 ± 5.00 (89)	0.6808
Pre-Procedure RVD (mm)	2.11 ± 0.24 (55)	2.14 ± 0.22 (90)	0.4615

[9] Mahoney EM, Jurkovitz CT, Chu H, Becker ER, Culler S, Kosinski AS, et al. Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *Jama* 2002; 288(15):1851-8.

[10] Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J* 2009; 157(1):141-8.

[11] Vaina S, Voudris V, Morice M-C, de Bruyne B, Colombo A, Macaya C, Richardt, G, Fajadet, J et al. Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularization in patients with multivessel coronary artery disease: Insights from ARTS I and ARTS II. *EuroInterv.* 2009; 4(4):492-501.

Subject Characteristics	Females (N=55) (M=55)	Males (N=89) (M=90)	P Value
Pre-Procedure MLD (mm)	0.55 ± 0.19 (55)	0.55 ± 0.20 (90)	0.9914
Pre-Procedure Percent Diameter Stenosis (%DS)	72.74 ± 8.31 (55)	72.90 ± 9.83 (90)	0.9150

Table 11 presents key clinical outcomes through 1 year in female and male subjects in the SPIRIT SV clinical trial. At 1 year, post-hoc analyses of the SPIRIT SV trial are limited with regards to conclusions that could be drawn regarding any differences in adverse event rates between female and male subjects due to the small sample size.

Table 11: Clinical Results for All Female and All Male Subgroups in the SPIRIT SV Clinical Trial through 1 year

SPIRIT SV	Females (N=55)	Males (N=89)
All Death	0.0% (0/51)	2.4% (2/85)
Cardiac Death	0.0% (0/51)	2.4% (2/85)
Non-Cardiac Death	0.0% (0/51)	0.0% (0/85)
Target Vessel MI	0.0% (0/51)	2.4% (2/85)
Cardiac Death or Target Vessel MI	0.0% (0/51)	4.7% (4/85)
Bleeding Complication	5.9% (3/51)	2.4% (2/84)
Stent Thrombosis		
Protocol defined	0.0% (0/51)	3.5% (3/85)
ARC definite + probable	0.0% (0/51)	2.4% (2/85)
TLF	11.8% (6/51)	5.9% (5/85)
Ischemia-Driven TLR	11.8% (6/51)	1.2% (1/85)
Ischemia-Driven TVR, non TL	7.8% (4/51)	4.7% (4/85)

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA supplement substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The safety and effectiveness of the XIENCE nano Everolimus Eluting Coronary Stent System are based on the results obtained from: evaluation of biocompatibility; *in vitro* engineering testing; coating characterization; chemistry, manufacturing and controls

information; *in vivo* animal testing; sterilization information; stability testing; and clinical studies. These tests revealed the following:

A. Safety Conclusions

The biocompatibility testing conducted on the XIENCE nano Stent System and the *in vivo* pharmacokinetics evaluation and *in vivo* animal testing conducted on the XIENCE V Stent System demonstrate that the acute and chronic *in vivo* performance characteristics of the product provide reasonable assurance of safety and acceptability for clinical use.

The *in vitro* engineering testing conducted on the stent and delivery systems demonstrated that the performance characteristics met the product specifications and the coating characterization testing adequately described the important attributes of the everolimus/polymer coating. The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released.

The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 12 months.

B. Effectiveness Conclusions

The results of the SPIRIT Small Vessel Registry showed that the primary composite endpoint of target vessel failure (defined as the composite of cardiac death, target vessel myocardial infarction and clinically-indicated target lesion revascularization) at one year was 8.1%, for which the upper limit of the one-sided 95% confidence interval was 13.03%, which met the prespecified performance goal of 20.4% ($p<0.0001$). This composite endpoint contains both safety and effectiveness components.

The clinical testing conducted demonstrated that the XIENCE nano Everolimus Eluting Coronary Stent System provides a reasonable assurance of safety and effectiveness when used in accordance with the instructions for use.

XIII. CDRH DECISION

CDRH issued an approval order on May 24, 2011.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.